Highlights of Novel Vaccination Strategies in Allergen Immunotherapy

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Abstract: Increasing safety while maintaining or even augmenting efficiency are the main goals of research for novel vaccine development and improvement of treatment schemes in allergen immunotherapy (AIT).1, 2, 3, 4 In spite of encouraging positive experiences,5 AIT still faces several problems related to worldwide standardization, its limited efficacy, potential severe side effects, low patient adherence, high costs, and long duration (3–5 years) of treatment. There have been many different approaches to improve the standardization, efficacy, and safety of AIT in the past, which have been continuously pursued during the past years.6, 7, 8 Currently, efforts on developing novel vaccines of AIT continue for the treatment of asthma,9 allergic rhinoconjunctivitis,10 bee venom allergy,11 and food allergy.12 Similar efforts are being undertaken for autoimmune diseases. Studies to offer prophylactic usage are also being performed.13 Regulatory issues represent an important aspect in this context14 and global and national strategies are being continuously developed.15,16 It is essential to develop strong collaborations with the regulatory authorities for extensive preventive usage of AIT vaccines and usage of pollen chambers for outcome evaluations to avoid slowing down of vaccine developments. Here, the authors summarize some current investigations aiming at further improvement of AIT vaccines (Table 1).

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Highlights of Novel Vaccination Strategies in Allergen Immunotherapy

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KEYWORDS

• Allergy • Allergen immunotherapy • AIT • Adjuvants • Allergoids
• Recombinant allergen peptides • Active immunization • Passive immunization

KEY POINTS

- The current aim is to improve allergen immunotherapy (AIT) to shorten duration of treatment, enhance efficiency, reduce side effects, and, ultimately, significantly increase the utilization of this curative treatment of allergy with high patient adherence and compliance.
- To increase the efficacy of AIT, allergens have been modified to facilitate their uptake and presentation, or have been coupled to innate immunostimulatory substances. New adjuvants have also been introduced recently.
- Hypoallergenic molecules (eg, allergoids and recombinant allergen peptides) have been developed to improve the safety profile of the vaccines.
- Administration of recombinant IgG_4 antibodies is a new, quick, passive immunization AIT strategy with remarkable efficiency.
- Recent mouse experiments suggest that it may be possible to develop AIT even for prenatal allergy prevention.

INTRODUCTION

Increasing safety while maintaining or even augmenting efficiency are the main goals of research for novel vaccine development and improvement of treatment schemes in allergen immunotherapy (AIT).[1–4] In spite of encouraging positive experiences,[5] AIT still faces several problems related to worldwide standardization, its limited efficacy,

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potential severe side effects, low patient adherence, high costs, and long duration (3–5 years) of treatment. There have been many different approaches to improve the standardization, efficacy, and safety of AIT in the past, which have been continuously pursued during the past years.[6–8] Currently, efforts on developing novel vaccines of AIT continue for the treatment of asthma,[9] allergic rhinoconjunctivitis,[10] bee venom allergy,[11] and food allergy.[12] Similar efforts are being undertaken for autoimmune diseases. Studies to offer prophylactic usage are also being performed.[13] Regulatory issues represent an important aspect in this context[14] and global and national strategies are being continuously developed.[15,16] It is essential to develop strong collaborations with the regulatory authorities for extensive preventive usage of AIT vaccines and usage of pollen chambers for outcome evaluations to avoid slowing down of vaccine developments. Here, the authors summarize some current investigations aiming at further improvement of AIT vaccines (**Table 1**).

NOVEL ALLERGEN FORMULATIONS AND ADJUVANTS

Adjuvants are add-on constituents of the vaccines, ideally increase the immunogenicity of the allergens to induce a quicker, stronger, and longer-lasting immune response; meanwhile also modulate the immune response to enhance allergen-specific T regulatory cell differentiation, immunoglobulin (Ig)G_4 antibody production, and, importantly, avoid T_H2-type response as well as anaphylaxis.

Coupling of allergens to innate immunostimulatory substances is primarily aimed at improving vaccine efficiency. These strategies include CpG oligonucleotide-conjugated allergens,[17] allergens coupled to viruslike particles,[18,19] carbohydrate-based particles,[20] and the use of monophosphoryl lipid A formulated with allergoid.[21] Encapsulation of allergens in nanoparticles enables us to design the immunomodulatory and depot effect of a complex vaccine very precisely.[22,23] Nanoparticles can have an adjuvant effect themselves (eg, viruslike particles), or various adjuvant molecules can be conjugated to or packed in the particles (eg, *Vibrio cholerae* neuraminidase on synthetic microparticles), and the physical-chemical characteristics of the particles determine the kinetics of the antigen release (eg, liposomes). Liposomes and microcrystalline tyrosine are promising new alternatives of the widely used aluminum hydroxide (alum) adjuvant.

Sublingual administration of an allergen together with α-galactosylceramide-liposomes increased the therapeutic performance of the vaccine in mouse model of allergic rhinitis.[24] High-affinity glycan ligand of the inhibitory receptor CD33 and the allergen, packed in liposomal nanoparticles, was able to suppress immunoglobulin (Ig)E-mediated activation of mast cells and, thus, was shown to be efficient in preventing anaphylaxis in transgenic mice bearing human CD33-expressing mast cells.[25] Such approaches may help to increase the safety of AIT.

Microcrystalline tyrosine, an alternative depo adjuvant composed of nonessential amino acid L-tyrosine, is a second-generation adjuvant currently used for AIT in humans (eg, Pollinex, Acarovac Plus).[26] It is proven to be safe for human use,[27] and efficiently induces IgG_4 production and reduces symptoms in house dust mite (HDM) subcutaneous immunotherapy (SCIT).[26]

Microcrystalline tyrosine-adsorbed grass pollen allergoid (Pollinex quattro) enhanced with monophosphoryl lipid A, a second-generation immunomodulatory adjuvant, had a beneficial long-term effect as well.[28]

Recombinant allergen peptides, selected to have advantageous safety profile are generally less immunogenic. Therefore, various carrier systems, typically of microbial origin, have been developed.[29] Promising new approaches include *Vibrio cholerae*

Table 1
Novel AIT vaccine developmental strategies currently being pursued

Type of the Vaccine/Approach	References
Coupling of allergens to innate immunostimulatory substances	
CpG oligonucleotide-conjugated allergens	17
Allergens coupled to viruslike particles	18,19,32,33
Carbohydrate-based particles	20
Vibrio cholerae neuraminidase on allergen-loaded synthetic microparticles	29
Fusion of nonallergenic peptides and PreS protein from hepatitis B virus	34,35
Fusion of nonallergenic peptides and tetanus toxoid	36
Novel adjuvants	
Monophosphoryl lipid A formulated with allergoid	21
Microcrystalline tyrosine	26,27
Proteoliposome adjuvant from *Neisseria meningitidis*	30
α-Galactosylceramide containing liposomes	24
Encapsulation of allergens in micro-/nanoparticles	
Carbohydrate-based particles	20
α-Galactosylceramide containing liposomes	24
CD33 ligand and the allergen packed in liposomal nanoparticles	25
V cholerae neuraminidase on allergen-loaded synthetic microparticles	29
Allergoids and recombinant allergens	
Monophosphoryl lipid A formulated with allergoid	21
Allergen extracts modified with glutaraldehyde	40
Fusion of nonallergenic peptides and PreS protein from hepatitis B virus	34,35
Fusion of nonallergenic peptides and tetanus toxoid	36
Recombinant T-cell epitope peptides	43
Allergen fragments	44
Recombinant allergen hybrids	45
Conjugation of allergoids to nonoxidized mannan	51,52
Fusion of allergens with other immune response modifiers	
CD33 ligand and the allergen packed in liposomal nanoparticles	25
MAT-vaccine	37,38
Conjugation of allergoids to nonoxidized mannan	51,52
Novel routes of administration	
Intralymphatic AIT	37,38,60
Epicutaneous AIT	59
Combination of AIT with biologicals	
Administration of anti-IgE	55–58
Novel administration protocols	
Passive immunization	69
Prenatal preventive vaccination	68,70

Considering that certain approaches may include different strategies, some of the vaccines are mentioned in multiple categories.

Abbreviations: AIT, allergen immunotherapy; Ig, immunoglobulin; MAT, modular antigen translocation.

neuraminidase, as an immunomodulatory agent, on allergen-loaded synthetic microparticles[30]; proteoliposome from *Neisseria meningitidis* as an adjuvant for HDM allergy vaccine[31]; and utilization of viruslike particles to enhance uptake of the allergen by antigen-presenting cells.[32] A single dose of allergen Fel d 1-linked viruslike particles is able to prevent type I hypersensitivity response in mice.[33,34] Fusion proteins consisting of nonallergenic peptides from the 4 major timothy grass pollen allergens and the PreS protein from hepatitis B virus as a carrier efficiently reduced T-cell proliferation and proinflammatory cytokine release, while increased blocking IgG activity.[35] Engineered recombinant fusion proteins consisting of nonallergenic peptides of the allergens and microbial components, like hepatitis B PreS protein[36] or partial fragment of a tetanus toxoid molecule,[37] seems to be safe and efficient in model systems.

In a novel approach, the major cat allergen (Fel d 1) was modified in a way that its uptake and presentation by professional antigen-presenting cells was highly improved. Human immunodeficiency virus transacting activator of transcription (TAT)-derived membrane translocation domain was used to enhance entry to cells, and a truncated peptide of the invariant chain was used to increase antigen presentation.[38,39] This modular antigen translocation (MAT)-Fel d 1 vaccine is efficiently internalized and potently presented to T cells by antigen-presenting cells, which stimulated T-cell responses in 100 times lower doses compared with native allergens. In a double-blind, placebo-controlled clinical trial, the MAT-Fel d 1 vaccine was administered in 3 increasing doses into inguinal lymph nodes at 4-week intervals. In addition to a good safety profile, only 3 doses of MAT-Fel d 1 intra-lymph node vaccination induced clinical tolerance to nasal cat allergen challenge in parallel with T-cell tolerance and increased serum IgG_4 and interleukin (IL)-10 levels.[38,39] Currently this approach is being pursued for veterinary vaccine development.

ALLERGOIDS, RECOMBINANT ALLERGENS

Targeting T cells to induce T-cell tolerance and bypassing IgE binding to avoid IgE-mediated side effects is an essential approach in AIT.[40] To improve AIT safety, the primary aim is to use hypoallergenic molecules to prevent severe complications such as anaphylaxis. Currently, there are many modified allergen preparations (allergoids) in the market with decreased IgE binding activity. Chemical modification of allergen extracts (eg, with glutaraldehyde[41]) aims to prevent IgE cross-link with conformational epitopes, while linear epitopes are preserved. To accomplish this aim, several successful new approaches have been developed,[42,43] including mixture of T-cell epitope peptides,[44] allergen fragments,[45] fusion proteins,[36,37] and recombinant allergen hybrids.[46] The prototype of this approach is peptide immunotherapy that uses linear T-cell epitope peptides, and has shown promising results,[47,48] although it still faces challenges in phase III clinical trials.[49–51] All of these allergoid preparations enable the administration of the allergens in higher doses to efficiently induce T-cell tolerance without the risk of anaphylaxis.[40] Conjugation of allergoids to nonoxidized mannan facilitates their uptake by antigen-presenting cells.[52,53]

Some of the clinically significant allergens, however, may be poorly represented in allergen extracts. Development of molecular vaccines, based on recombinant allergen components, helps to overcome the limitations of the vaccines based on natural allergen extracts.[54] Identification of immunodominant molecular components of the allergens is an important initial step of the development of such AIT approaches.[55]

ADD-ON THERAPIES AND NEW PROTOCOLS

Combination of conventional or novel methods of AIT with biological immune response modifiers is a promising new therapeutic approach. Anti-IgE combined with AIT has been evaluated in several studies. Significant decrease in the risk of anaphylaxis and improved rescue medication scores were observed during rush immunotherapy with a quicker dose increment and reach of the maintenance dose.[56,57] Accumulating evidence suggests that anti-IgE treatment is a valuable add-on to AIT for airway allergies, especially to prevent adverse events in the build-up phase and improve safety profile in cases in which the designated maintenance dose is not tolerated by the patient.[58,59] Other possible combinations include anti-IL-4 or anti-IL-13 as well as their receptor antagonists.

Different routes of vaccine administration also have been proposed to improve efficacy and safety. Intralymphatic vaccination and epicutaneous vaccination are recently pursued novel strategies. Both showed similar efficacy to SCIT in grass pollen allergy, however, that has been reached with fewer injections and lower total allergen doses.[60] Intralymphatic administration induces T-cell tolerance or strong T_H1 responses depending on the type of vaccine used.[39,61]

Meta-analysis of the double-blind, placebo-controlled trials has shown that sublingual immunotherapy (SLIT) is safe and clinically efficacious with a treatment benefit approximately half of that achieved with SCIT.[62] Disease-modifying effects of SLIT have been confirmed in large-scale randomized, double-blind, placebo-controlled trials also in children[63–68]; and even its preventive administration has been proposed.[69]

In an exciting, current study, cat-allergic patients were treated with a single dose of 2, fully human, recombinant IgG_4-blocking antibodies specific for Fel d 1, the major cat allergen. This treatment resulted in a rapid and sustained reduction in clinical symptoms after nasal allergen provocation test, suggesting a new, quick, passive AIT strategy for allergies.[70] Treatment-emergent adverse events were closely monitored during the study, and there was neither any difference in the frequency of the adverse events between antibody-treated and placebo group, nor did any severe adverse event occur in relation to the IgG_4 antibody treatment.[70]

In a recent mouse experiment, the administration of anti-IgE antibody during pregnancy caused long-term IgE-class–specific immunosuppression in the offspring that was able to prevent allergic sensitization. These results suggest that it may be possible to develop a vaccination strategy aiming prenatal allergy prevention.[71]

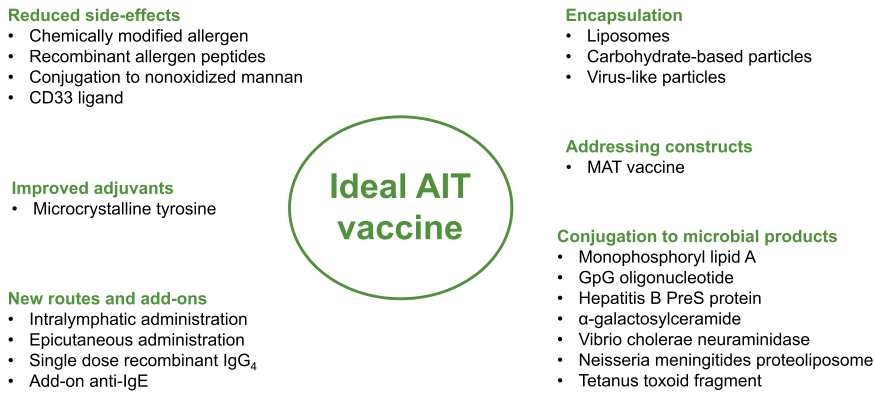

Fig. 1. Strategies for development of a more safe, efficient, and reliable vaccine for AIT.

SUMMARY

Intensive efforts have been invested to improve AIT vaccines by making them more efficient, convenient, and safe[2,16] (**Fig. 1**). Still, fewer than 10% of allergic patients choose to receive AIT.[72] Besides the fear from potential side effects and poor adherence due to long duration of treatment,[73] the possible cause of weak overall, population-wide efficiency of AIT is that not all the potential influencing factors were considered during the development of AIT strategies, because of lack of knowledge. Identification of good biomarkers predicting beneficial vaccine immune response is still an unmet clinical need; however, it is under intensive investigation.[74] Better understanding of the immune response to vaccines will hopefully enable us to develop more efficient AIT strategies specifically tailored to allergic disease endotypes.[75]

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